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Disruption and lateralization of cerebellar–cerebral functional networks in right temporal lobe epilepsy: A resting-state fMRI study

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ABSTRACT

Numerous studies have highlighted important roles for the cerebellum in cognition and movement, based on numerous fiber connections between the cerebrum and cerebellum. Abnormal cerebellar activity caused by epileptic discharges has been reported in previous studies, but researchers have not clearly determined whether aberrant cerebellar activity contributes to the disruption of the cerebellar–cerebral networks in right temporal lobe epilepsy (rTLE). Here, thirty patients with rTLE and 30 age- and sex-matched healthy controls (HCs) were recruited. All participants underwent the Attention Network Test (ANT) and resting-state functional magnetic resonance imaging (rs-fMRI) scanning. Cerebellar functional networks were extracted and analyzed by defining seeds in the cerebellum. A correlation analysis was performed between attentional performance and voxels that showed differences in functional connectivity (FC) in patients compared with HCs. Relative to HCs, patients exhibited significantly decreased FC in the dentate nucleus (DN) network (right DN with the left postcentral gyrus, left precentral gyrus, left cuneus, and left calcarine gyrus) and motor network (right cerebellar lobule V with the right putamen) and increased FC in the executive control network (right cerebellar crus I with the right inferior parietal lobule). Alerting, orienting, and executive control performances were impaired in patients with rTLE. Furthermore, the executive control effect was significantly correlated with aberrant FC strength between the right DN and the left precentral/postcentral gyrus. Our findings highlight that the disrupted cerebellar–cerebral functional network ipsilateral to the epileptogenic focus causes both impairments in and compensatory effects on attentional deficits in patients with rTLE. These findings contribute to our understanding of the cerebellar damage caused by epileptic discharges and the corresponding effect on attentional performance.

1. Introduction

Temporal lobe epilepsy (TLE) is defined as focal epilepsy characterized by seizures that mainly originate from the hippocampus. Although the epileptogenic focus is located in the temporal lobe, many studies have revealed that the transmission of epileptic discharges results in abnormalities in the cerebral cortex and subcortical areas in TLE [1–3]. These abnormalities have been widely observed, not only in the local volume, but also in structural and functional connectivity (FC) within different brain regions. Thus, TLE has increasingly been considered a condition associated with a network-level disruption in recent years [2].

The cerebellum, a relatively independent modular structure, has gradually attracted increasing attention. The lateral cerebellum is differentially connected to the contralateral cerebral cortex, including the classic motor brain regions (primary motor and premotor area), nonmotor targets (posterior parietal and prefrontal area), via dentate nuclei (DNs), the contralateral thalamus, and basal ganglia [4,5]. Based on accumulating evidence, epileptic discharges contribute to structural and functional abnormalities in the cerebrum and cerebellum in TLE. A mouse model of TLE with a responsive optogenetic intervention revealed that the cerebellum is a crucial intervention target that inhibits temporal lobe seizures following the induction of evoked potentials in the hippocampus via direct or indirect connections [6]. In mesial TLE, gray matter volume showed significant reductions in the ipsilateral hippocampus and extrahippocampal structure. Intriguingly, the hippocampus and thalamus exerted prominent causal effects on the activity of the cerebellum and prefrontal cortex in structural network as determined by a Granger Causality Analysis [7]. Patients with mesial TLE and hippocampal sclerosis manifested decreased regional homogeneity in the bilateral posterior cerebellar lobe [8]. Furthermore, the cerebellum

Abbreviations: rTLE, right temporal lobe epilepsy; HC, healthy control; rs-fMRI, resting-state functional magnetic resonance imaging; ANT, Attention Network Test; FC, functional connectivity; DN, dentate nucleus; ROIs, regions of interest; MNI, Montreal Neurological Institute; RT, reaction time.

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showed positive or negative activities in patients with TLE performing different cognitive tasks compared with healthy controls (HCs) [9]. In summary, the cerebellum not only regulates and inhibits epileptic discharges but is also one of the brain targets injured in TLE.

Notably, the DN, the largest deep cerebellar nuclei, is the relay station of efferent and afferent nerve fibers from or to the cerebellum. Thus, abnormalities in the DN may contribute to cerebellar-cortical disconnection and corresponding clinical symptoms associated with motor control, cognitive function, and emotional processing. Based on compelling evidence, the DNs are damaged in many diseases, including multiple sclerosis, autism spectrum disorders, and progressive supranuclear palsy (PSP). Patients with PSP presenting with cerebellar ataxia exhibited increased frequency of heterogeneous regions in the DNs, which play an etiological role in the impairment in postural stability [10]. In patients with multiple sclerosis, the FC network of the DNs showed decreased or increased connectivity with the subcortical regions, cerebral cortex, and cerebellar cortex [11,12]. These disruptions in connectivity were correlated with worse balance performance and cognitive dysfunction. However, researchers have not clearly determined whether the DN networks are disrupted in TLE. Separate cerebellar lobules, the functional domains of the cerebellum, underlie the DN networks by projecting fibers to distinct areas of the cerebral cortex via the DNs. These cerebral–cerebellar circuits participate in disparate brain intrinsic networks, i.e., cerebellar crus I and crus II in the executive control network, crus II and lobule IX in the default mode network, and lobule IV-V in the somatomotor network. Abnormal functions of cerebellar subregions have been revealed in neuropsychiatric disorders, such as schizophrenia [13,14], depression [15], and autism spectrum disorder [16], and are correlated with cognitive deficits in patients. Attentional function is the basis of cognitive function and is composed of alerting, orienting, and executive functions [17]. Numerous studies have reported attention deficits in patients with TLE. In the verbal attention test, patients with mesial TLE, particularly patients in the pharmacoresistant group, showed worse performance than healthy subjects [18]. Attention dysfunction in subjects with TLE has also been observed in the lithium-pilocarpine model, in which rats displayed impairment in attention performance, and these disturbances appeared to be related to neuronal loss in the hippocampus [19]. As shown in our previous study, patients with right temporal lobe epilepsy (rTLE) exhibited an obvious alerting deficit and executive deficit, as revealed by decreased scores on the Digit Symbol, Digit Span, Verbal Fluency tests, and Attention Network Tests (ANTs) [20,21]. Additionally, attentional deficits in patients with TLE are closely associated with impairments in cerebral cortical or subcortical structures, such as the uncinate fasciculus, thalamic, and ascending reticular activating system [21–23]. However, the mechanism underlying alterations in the cerebellar–cerebral networks and especially how these changes affect attentional dysfunction in patients with TLE remain unclear.

In the current study, we aimed to investigate features of cerebellar–cerebral FC of the DN networks and intrinsic cerebellar networks by applying a seed-based FC analysis to patients with rTLE and HCs. The bilateral DNs and other cerebellar seeds were chosen as regions of interest (ROIs). Attentional function was assessed using the ANT. To our knowledge, this study is the first to investigate the cerebellar–cerebral networks from the perspective of the cerebellum in rTLE. We hypothesized that the cerebellar–cerebral FC in patients with rTLE would be significantly different from HCs, and that certain patterns of abnormal FC would participate in the pathological process of attention deficit.

2. Materials and methods

2.1. Participants

All participants were recruited from the epilepsy clinic of the First Affiliated Hospital of Guangxi Medical University. This study was approved by the hospital's Medical Research Ethics Committee. Written informed consent was provided by all participants. Thirty right-handed patients with rTLE were diagnosed by two epilepsy specialists according to clinical characteristics, electroencephalograms (EEGs), and an imaging examination. Patients were required to satisfy at least two of the following inclusion criteria: 1) typical symptoms of epileptic seizures indicating that the epileptogenic focus was located in the temporal lobe; 2) magnetic resonance imaging (MRI) showed that the right hippocampus was atrophy, sclerosis, or other abnormalities in the right temporal lobe; and 3) an EEG examination revealed that epileptic discharges originated from the right temporal lobe. The following exclusion criteria were used: 1) a Mini-Mental State Examination (MMSE) score less than 24; 2) a diagnosis of severe mental or neurological diseases; and 3) patients who were unable to cooperate well enough to complete all procedures in this experiment.

Thirty right-handed HCs without a history of mental or neurological diseases were enlisted from the community. Age, sex, education level, and MMSE scores were matched with that of patients.

2.2. Magnetic resonance (MR) imaging acquisition

Imaging was performed with an Achieva 3.0 T MRI system scanner (Philips, Amsterdam, The Netherlands). For resting-state functional MRI (rs-fMRI) scanning, participants were instructed to remain in an awake and relaxed state, to avoid thinking anything about a specific topic, and to keep their eyes closed. The rs-fMRI scans were acquired using a gradient-echo planar image sequence (repetition time (TR), 2000 ms; echo time (TE), 30 ms; flip angle, 90°; matrix, 64×62; slice thickness, 5 mm; slice gap,1 mm; field of view, 220×220 mm^2; voxel size, 3.44 mm × 3.44 mm × 5.00 mm; number of slices, 31).

2.3. Imaging data preprocessing

The rs-fMRI data were preprocessed using Data Processing & Analysis for Brain Imaging (DPABI) software (http://rfmri.org/dpabi) on the Matrix Laboratory (MATLAB) platform. The first ten time points were discarded to maintain magnetization equilibrium. Surplus volumes were processed as follows: slice timing and brain realignment correction, normalization to the echo-planar imaging template in Montreal Neurological Institute (MNI) coordinates, resampling to a resolution of 3 mm × 3 mm × 3 mm, spatial smoothing with a 6-mm full-width at half maximum Gaussian kernel, bandpass filtering within 0.01–0.08 Hz, regression of covariates representing 12 head motion parameters, and averaging signals from white matter and cerebrospinal fluid. Data were excluded if displacement was >2 mm and angular rotation was >2° in any direction.

2.4. Seed-based FC analysis

The seed-based FC analysis was performed to extract the cerebellar–cerebral functional network using RESTplus software (http://restfmri.net/forum/RESTplusV1.2). The left/right DN [12] (left DN: $x = -17$, $y = -58$, $z = -35$; right DN: $x = 17$, $y = -58$, $z = -35$; 4 mm radius) and cerebellar subregions (6 mm radius) related to intrinsic brain networks, including the default mode network (cerebellar crus II: left $x = -32$, $y = -76$, $z = -34$; right $x = 34$, $y = -80$, $z = -35$ and cerebellar lobule IX: $x = 0$, $y = -55$, $z = -49$), executive control network (cerebellar lobule I: left $x = -12$, $y = -78$, $z = -28$; right $x = 12$, $y = -78$, $z = -28$), motor network (cerebellar lobule V: left $x = -20$, $y = -50$, $z = -24$; right $x = 22$, $y = -52$, $z = -22$), and affective-limbic network (cerebellar lobule VI: left $x = -26$, $y = -64$, $z = -34$; right $x = 26$, $y = -64$, $z = -34$ and cerebellar vermis: $x = -4$, $y = -80$, $z = -34$), were defined as ROIs in MNI coordinates for the global FC analysis. Each ROI was used to define an average time course at the individual level. Then, Pearson's correlation coefficients were calculated between the time courses of each ROI and signal time series of each voxel across

the whole brain to generate an ROI-FC map for each participant. The ROI-FC map was subjected to Fisher's r-to-z transformation to generate a z-score FC map to improve the normality of correlation coefficients. Z-score FC maps within the group with rTLE and control group were statistically analyzed using a one-sample *t*-test (Gaussian random field (GRF) corrected, voxel significance: $p < 0.005$, cluster significance: $p < 0.05$). To extract the DN networks within the control group, a more stringent statistical analysis was performed (family-wise error (FWE) corrected, cluster significance: $p < 0.05$) using the Statistical Parametric Mapping version12 (SPM12) software. (http://www.fil.ion.ucl.ac.uk/spm). After the one-sample *t*-test, a mask was merged from the statistically significant zFC maps of group with rTLE and HC group for further between-group comparisons. A two-sample *t*-test (GRF corrected, voxel significance: $p < 0.005$, cluster significance: $p < 0.05$) was performed to investigate FC strength with significant differences between the group with rTLE and control group, with age, gender, and educational level serving as nuisance covariates.

2.5. Neuropsychological testing

Attentional function is divided into three subsystems, including the alerting, orienting, and executive control networks. The ANT, a neuropsychological testing method, was applied to assess each participant's attentional performance [17]. The ANT, with 96 formal trials in 3 modules, is based on the E-Prime platform. Before the formal test, each participant was first familiarized with the procedure and allowed to practice for 24 trials. Participants were tested in a quiet and undisturbed environment and instructed to focus on a cross in the center of screen throughout this test. The four cue signals indicating forthcoming target signals consisted of a double asterisk, a central asterisk, an asterisk above or below, and no asterisk. The stimuli on the computer screen consist of one target arrow in the center and another four arrows for interference. Two different directions randomly appeared between the central and interfering arrows in congruent or incongruent directions. According to the direction of the target arrow, the mouse button with the corresponding direction was pressed. The entire test lasted approximately 25 min. The mean reaction time (RT) was recorded by the ANT software. The executive control effect was calculated by subtracting the mean RT of congruent signal conditions from the mean RT of incongruent signal conditions. The orienting effect was computed by subtracting the mean RT of the spatial cue conditions from the mean RT of the center cue. The alerting effect was calculated as follows: subtract the mean RT of double cue conditions from the mean RT of no cue conditions. The double cue condition reflects phasic alertness, and the no cue condition indicates intrinsic alertness. A larger value for the executive control effect represents worse executive control function, while larger values for the alerting effect and orienting effect represent better alerting and orienting performance [24].

2.6. Statistical analysis

Statistical analyses were conducted using Statistical Package for Social Science (SPSS) 16.0 software. Data are reported as means ± standard deviations. The differences in age, education level, alerting effect, orienting effect, and executive control effect between the group with rTLE and HC group were analyzed using an independent two-sample *t*-tests, while differences in gender were analyzed using a chi-square test. A correlation analysis was performed to investigate the relationships between cerebellar–cerebral FCs with significant difference and attentional performance in patients with rTLE. $p < 0.05$ was defined as statistically significant.

3. Results

3.1. Demographic and clinical characteristics

The demographic data and clinical characteristics of 30 patients with rTLE and 30 HCs are presented in Table 1. No differences in age, gender, or educational levels were observed. Attentional performances were assessed using the ANT. Executive control and orienting functions were apparently impaired with increased (rTLE: 100.39 ± 27.46 ms vs. HC: 77.86 ± 15.74 ms; $p = 0.000$) and decreased (rTLE: 33.54 ± 19.08 ms vs. HC: 44.74 ± 18.58 ms; $p = 0.025$) mean effect RTs, respectively. Significant difference in the alerting effect was not observed between patients and HCs (rTLE: 41.90 ± 13.42 ms vs. HC: 44.29 ms ± 15.44 ms; $p = 0.524$). However, the no cue (rTLE: 694.26 ± 94.47 ms vs. HC: 615.40 ± 55.69 ms; $p = 0.000$) and double cue (rTLE: 648.36 ± 89.93 ms vs. HC: 574.45 ± 53.97 ms; $p = 0.000$) conditions of the alerting network produced a significantly longer mean RT in the group with rTLE than in the HC group.

Table 1
Demographic and clinical characteristics of all participants.

	rTLE	HCs	p-Value
Gender (M/F)	15/15	14/16	0.796
Age (years)	27.77 ± 6.41	25.77 ± 4.72	0.174
Education (years)	12.77 ± 3.64	13.23 ± 3.06	0.593
Duration (years)	8.13 ± 5.83	–	–
Executive control effect RT (ms)	100.39 ± 27.46	77.86 ± 15.74	0.000
Alerting effect RT (ms)	41.90 ± 13.42	44.29 ± 15.44	0.524
No cue RT (ms)	694.26 ± 94.47	615.40 ± 55.69	0.000
Double cue RT (ms)	648.36 ± 89.93	574.45 ± 53.97	0.000
Orienting effect RT (ms)	33.54 ± 19.08	44.74 ± 18.58	0.025

rTLE, right temporal lobe epilepsy; HCs, healthy controls; F, female; M, male; RT, reaction time. Data are presented as means ± standard deviations. Statistical significance was set at $p < 0.05$.

3.2. FC in the DN

In the within-group analysis, a normal DN FC network was observed in the HC group. As shown in Fig. 1, the left and right DN both exhibited bilateral and similar positive FC with the prefrontal cortex, primary motor cortex, supplementary motor cortex, temporal–parietal and occipital cortex, cingulum, basal ganglia, thalamus, brainstem, and cerebellum in the HC group.

In the between-group analysis, lower FC in the DN network emerged in the patients with rTLE compared with the HC group. Brain regions showing decreased FC with the right DN were mainly located in the left calcarine gyrus, left postcentral gyrus, left precentral gyrus, and left cuneus (Fig. 2 and Table 2). No significant differences in FC to various brain regions were observed for the left DN.

3.3. Cerebellar subnetworks

In addition to DNs, several ROIs in the cerebellum related to the default mode network, motor network, executive control network, and affective-limbic network were defined for further cerebellar–cerebral FC analyses. In contrast to HCs, enhanced FC was observed between right cerebellar crus I and the right inferior parietal lobule in the executive control network, and reduced FC emerged between right cerebellar lobule V and the right putamen in the motor network in patients with rTLE, as shown in Fig. 3 and Table 2. Other cerebellar networks did not show altered FC in patients with rTLE compared with the HC group.

3.4. Correlation analysis

A correlation analysis was performed to investigate the relationship between altered brain regions with significantly different FC with DNs or other cerebellar seeds and clinical variables, including attentional performance, disease duration, and seizure frequency, in patients with rTLE. A significant positive correlation was observed between the executive control effect and FC between the right DN and the left precentral/postcentral gyrus ($p = 0.011$, $r = 0.459$; Fig. 4).

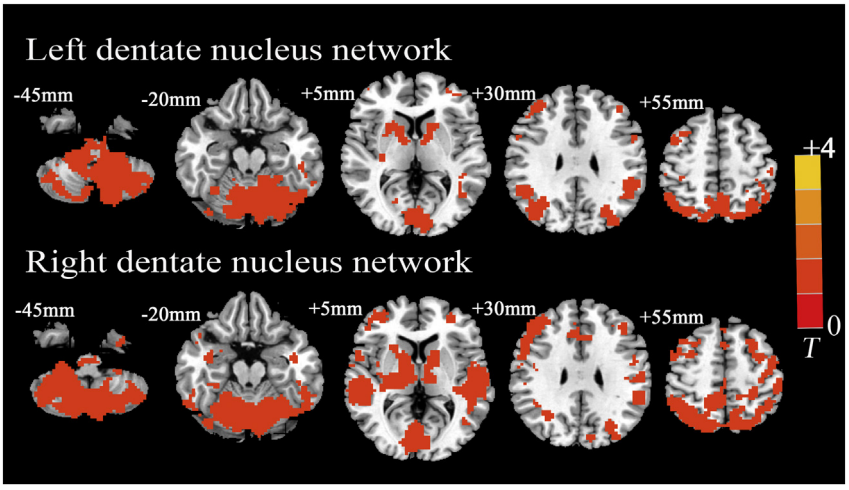

Fig. 1. The DN functional networks in healthy controls. The DN functional networks involve the prefrontal cortex, primary motor cortex, supplementary motor cortex, temporal–parietal and occipital cortex, cingulum, basal ganglia, thalamus, brainstem, and cerebellum. Warm colors show positive functional connectivity. FWE corrected, cluster level: $p < 0.05$. DN, Dentate nucleus.

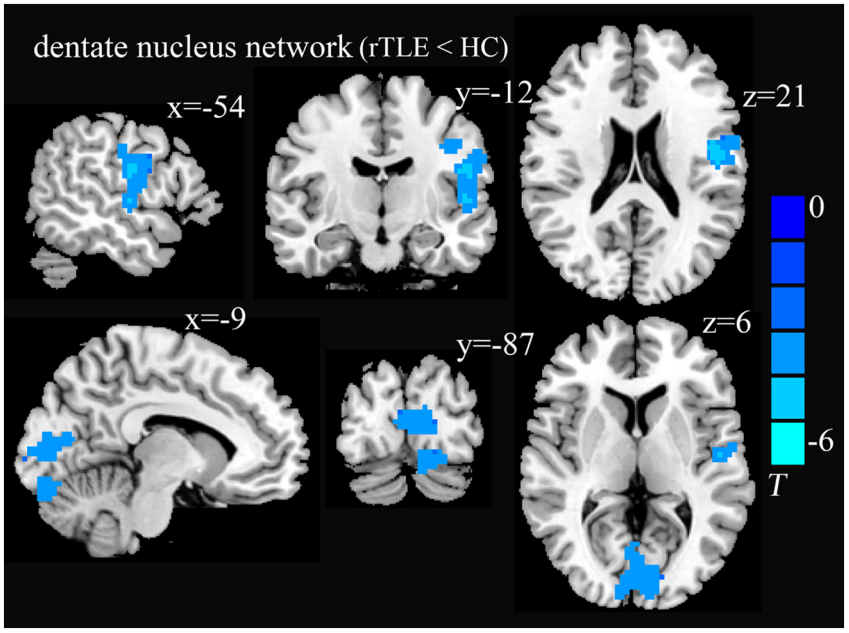

Fig. 2. Altered right DN network in patients with rTLE relative to healthy controls. Decreased FC with the right DN was mainly located in the left precentral gyrus, postcentral gyrus, cuneus, and calcarine gyrus. GRF corrected, voxel level: $p < 0.005$, and cluster level: $p < 0.05$. Color bar: cool colors represent negative FC. DN, dentate nucleus; rTLE, right temporal lobe epilepsy; FC, functional connectivity.

4. Discussion

In this study, we performed an FC analysis to investigate the cerebellar–cerebral networks in patients with rTLE. Compared with HCs, the group with rTLE exhibited decreased FC in the DN network (right DN with the left postcentral gyrus, left precentral gyrus, left cuneus, and left calcarine gyrus) and motor network (right cerebellar lobule V with the right putamen), but increased FC in the executive control network (right cerebellar crus I with the right inferior parietal lobule). These disrupted FC patterns were prominently characterized by lateralization and were located in right cerebellar seeds. Furthermore, attentional function was impaired in patients, and the executive control

Table 2
Between-group differences in cerebellar–cerebral functional connectivity (rTLE vs HC).

Seed	Brain region	Voxels	t-Value	MNI coordinates (x, y, z)
Dentate nucleus_R	Precentral gyrus_L/postcentral gyrus_L	322	−4.3115	−54, −12, 21
	Cuneus_L, calcarine gyrus_L	442	−3.6903	−9, −87, 6
Cerebellar crus I_R	Inferior parietal lobule_R	239	4.0931	57, −39, 45
Cerebellar lobule V_R	Putamen_R	235	−4.9711	27, 9, 0

rTLE, right temporal lobe epilepsy; HC, healthy control; R, right; L, left; MNI, Montreal Neurological Institute. Gaussian random field corrected, voxel level: $p < 0.005$, and cluster level: $p < 0.05$.

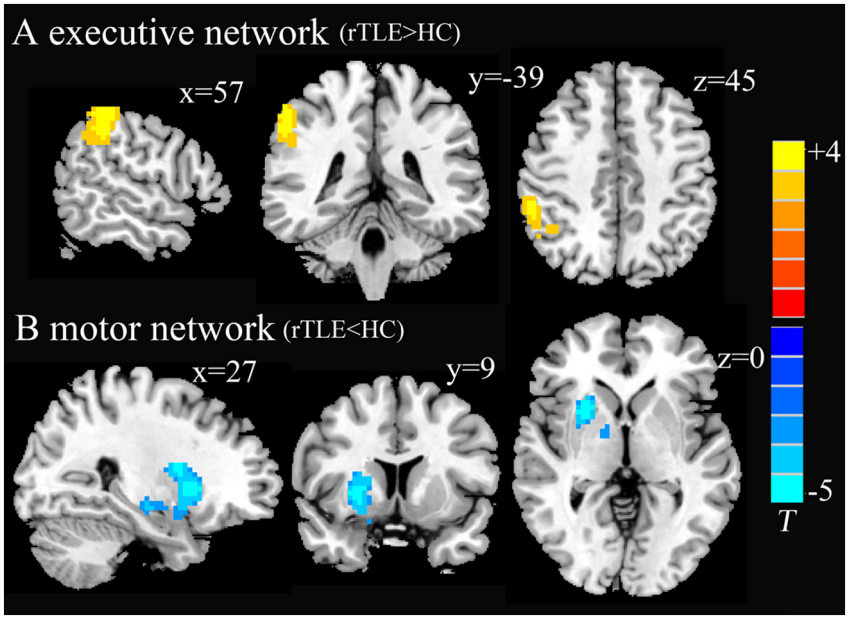

Fig. 3. Differential cerebellar–cerebral FC maps in patients with rTLE compared with healthy controls. A, Increased FC between the right cerebellar crus I and right inferior parietal lobule in the executive control network. B, Decreased FC between the right cerebellar lobule V and the right putamen in the motor network. GRF corrected, voxel level: $p < 0.005$, and cluster level: $p < 0.05$. Color bar: warm color represents positive FC, cool color represents negative FC. FC, functional connectivity; rTLE, right temporal lobe epilepsy.

effect was significantly correlated with FC strength between the right DN and left precentral/postcentral gyrus. These results indicate that the cerebellar–cerebral functional networks were disrupted with lateralization to the epileptogenic focus and contributed to attentional deficits in patients with rTLE.

The cerebellum is considered a relatively independent modular structure and is closely connected with the cerebral cortex and subcortical regions via the DNs [5,25]. Anatomically, streamlines in the cerebellar-cortical pathway principally reach the frontal, parietal, occipital, and temporal lobules [26]. In this study, we investigated the functional organization of the cerebellar–cerebral network by performing a voxel-wise analysis of DNs. Similar to previous studies, FC of the DNs is widespread, and mainly located in subcortical regions (e.g., cerebellum, brainstem, thalamus, and basal ganglia), sensorimotor (e.g., primary and supplementary motor cortices and the somatosensory area), and nonmotor cortical

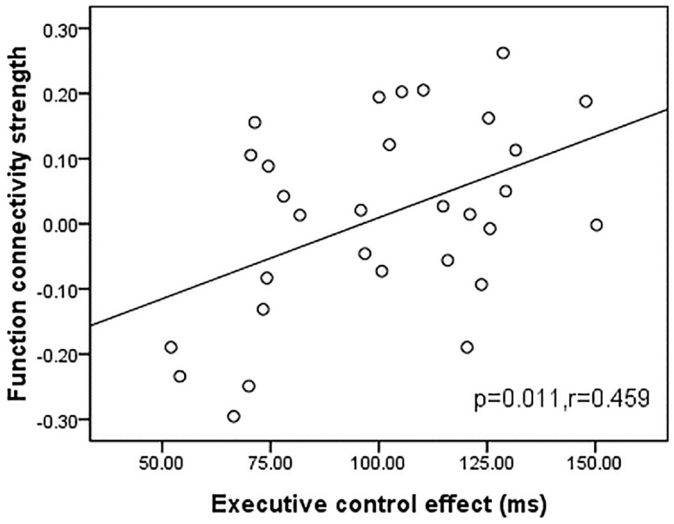

Fig. 4. The functional connectivity strength between the precentral/postcentral gyrus and right dentate nucleus exhibited significant correlation with the executive control effect in patients with rTLE. rTLE, right temporal lobe epilepsy.

areas (e.g., prefrontal and orbitofrontal cortices, inferior parietal lobule, superior temporal gyrus, occipital cortex, and cingulum) in HCs. These widespread connections between the DN and other brain regions confirm the role of the cerebellum in motor control and higher cognitive function. Compared with HCs, lower FCs were principally identified between the right DN and the left calcarine gyrus, left cuneus, left precentral gyrus, and left postcentral gyrus in patients with rTLE. Thus, the cerebellar–cerebral network was disrupted by epileptic discharges, consistent with previous reports. According to Zheng et al., patients with rTLE showed decreased FC of the right occipital lobe and cerebellum in the alertness-related network [27]. Angelo et al. applied a whole-brain cortical thickness analysis and observed significant thinning in the bilateral sensorimotor cortex, occipital cortex, and other areas in patients with TLE presenting mesial temporal sclerosis [28]. In another study, patients with TLE presenting hippocampal sclerosis exhibited to a reduced size of the postcentral gyrus, which was associated with impaired egocentric memory. In cognitive tasks (including memory, language, and executive tasks), patients with TLE showed disrupted activation in an extensive set of regions, such as the cerebellum, prefrontal cortex, frontal lobe, and postcentral gyrus [29]. According to multiple studies, numerous brain regions (e.g., the supplementary motor cortex, precentral gyrus, and bilateral temporal–occipital region) were highly activated by alertness-related tasks [27,30,31]. In the present study, our ANT results also showed impaired attentional function in patients with rTLE, and the executive control effect was correlated with aberrant FC between the right DN and the left precentral/postcentral gyrus. This finding was consistent with previous reports that the precentral and postcentral gyri not only integrate sensorimotor functions but also participate in cognitive processes. Taken together, epileptic discharges disrupted FC between the DNs and motor- and nonmotor-related cerebral regions, which indicate potential sensorimotor and cognitive dysfunction in rTLE.

The executive control network participates in goal-directed and complex activities, such as sustained attention, processing speed, fluency, perceptual reasoning, working memory, and dual-task management. The prefrontal lobe is the primary executive structure and constitutes the executive network by connecting with other cortical and subcortical regions (i.e., the parietal cortex, caudate nucleus, thalamus, anterior cingulate, and cerebellum) [32]. Cerebellar crus I is the predominant cerebellar

lobule connected with the prefrontal cortex and is involved in higher cognitive function, particularly executive control function. In the present study, patients with rTLE showed impairment in executive control function, with a prolonged RT for executive control effect and enhanced FC between the right cerebellar crus I and the right inferior parietal lobule. The inferior parietal lobule consists of the adjacent angular gyrus and supramarginal gyrus, and is closely associated with basic attentional processes of executive function [33,34]. The inferior parietal lobule and prefrontal cortex have been shown to display strong activation during executive processing, such as in the Wisconsin Card-Sorting Task and mindfulness meditation training [35,36]. In our previous studies, compared with HCs, patients with TLE exhibited decreased FC strength of the inferior parietal gyrus in the resting state or verbal working memory task [20,37]. As shown in the study by Shigetoshi et al., patients with medically intractable TLE who underwent subtemporal selective amygdalohippocampectomy showed an increase in postoperative glucose metabolism in a wide range of extratemporal regions of the brain, including the prefrontal lobules, superior temporal gyrus, and inferior parietal lobules; and this hypermetabolism was accompanied by better verbal memory and delayed recall scores in memory performance in patients [38]. In a FC analysis of the left hippocampus, patients with left TLE showed enhanced connectivity between the right inferior parietal lobule and left hippocampus, which was positively correlated with high memory retention scores [39]. Furthermore, accumulating evidence has revealed compensatory characteristics of the cerebellum in numerous diseases, such as Parkinson's disease [40], multiple sclerosis [12], major depression disorder [15], and Huntington's disease [41]. The compensatory effect of the cerebellum on attenuating clinical symptoms is primarily mediated by hypermetabolism, increased FC strength, and a larger volume under pathological conditions. Thus, we speculate that higher activity between the inferior parietal lobule and cerebellum crus I may exert a compensative effect on executive dysfunction in patients with rTLE.

The cerebellum and basal ganglia are traditionally regarded as important motor regulatory centers in the brain. The putamen projects to the primary motor cortex and is classically regarded as a primary component of the cortical-basal ganglia motor circuit [42,43]. In our study, decreased FC strength emerged between the right putamen and right cerebellar lobule V, the motor-related cerebellar cortex. Previous studies have verified that TLE decreases FC between the putamen and somatomotor cortex [44] and reduces the putamen volume [45]. Hetherington et al. reported a significant correlation between neuronal injury/loss in the putamen and neuronal loss in the ipsilateral hippocampus in patients with TLE, as evaluated by the ratio of *N*-acetyl aspartate to creatine. Additionally, compared with HCs, patients with TLE displayed difficulties in coordinated motor performance (such as manual dexterity, bimanual coordination, maintenance of a series of movements, and bimanual performance of asymmetrical movements in rapid succession) [46]. Combined with the findings from these investigations, we infer that decreased FC between the putamen and cerebellum contributes to deficits in motor coordination. Furthermore, this finding strengthens our awareness of pathologic lesions related to motor coordination that have emerged in cerebellum, and more meticulous examinations related to motor function are required in further investigations.

It is worth noting that cerebellar ROIs with significant differences in FC strength were mainly located in the right cerebellar hemisphere in rTLE. The cerebellum receives fibers primarily originating from the contralateral frontal, parietal, and occipital lobes. In particular, projections from the temporal lobe to the cerebellum are bilateral, but with an ipsilateral predominance [47,48]. Dentate nuclei act as output stations projecting efferent fibers to the cerebral cortex via the thalamus. Esther A et al. observed higher connection densities from the right DN than from the left DN to the thalamus in healthy participants using diffusion MRI and probabilistic tractography [49]. Thus, laterality in the anatomical connections between the cerebrum and cerebellum contributes to the increased vulnerability of the right cerebellar hemisphere to epileptic discharges generated from the ipsilateral temporal lobule in rTLE. Our results showing ipsilateral FC changes in the cerebellum were consistent with previous studies. A diffusion tensor imaging (DTI) study revealed decreased fractional anisotropy in the cerebellum ipsilateral to the epileptogenic focus in patients with TLE [50]. In an EEG-fMRI analysis, activation of the ipsilateral cerebellar cortex was observed in patients with TLE, whereas this change was not obvious in patients with frontal lobe epilepsy [51]. A voxel-based morphometry study revealed a significant reduction in the gray matter volume of the ipsilateral cerebellum in right mesial TLE [45].

Several potential limitations of the present study should be considered. In the current study, the slice thickness/gap was relatively large compared with that used in previous studies and may result in the dropout of some imaging signals. And, it is of great importance to acquire more interpretable and credible results using more precise raw imaging data by setting a smaller slice thickness/gap in our further studies. Here, we only investigated the DNs and certain cerebellar lobules that participate in predominant intrinsic brain networks. Other deep cerebellar nuclei and regions of the cerebellar cortex are worth studying to further investigate the effects of the cerebellum on motor and cognitive function in patients with TLE. In addition, we conducted a limited neuropsychological evaluation of attentional function in patients with TLE. Therefore, we should investigate the performance of other higher-level cognitive and motor tests in the future. And, performing the fMRI scan during cognition-related tasks would allow us to directly and clearly understand the correlations between alterations in cerebellar–cerebral FC and cognitive functions. Furthermore, it will provide more evidence on the pathological mechanism of cerebellar impairments by investigating the effects of heterogeneous clinical characteristics (e.g., disease duration, antiepileptic drugs, seizure types, and seizure frequency) and structural connectivity alterations on cerebellar–cerebral FC in TLE. Finally, as mentioned above, the cerebellum might exert a significant compensatory effect on delaying disease progression or alleviating clinical symptoms in numerous neuropsychological diseases. Thus, longitudinal observations are needed in the future to identify pathophysiological changes in brain regions that particularly illustrate the potential mechanisms by which the cerebellum compensates for the pathophysiological dysfunction.

5. Conclusions

To our knowledge, this study is the first to investigate alterations in the FC of cerebellar–cerebral networks by applying cerebellar seeds in the resting state in patients with rTLE. We observed abnormal FC between cerebellar seeds ipsilateral to the epileptogenic focus and cerebral areas involved in motor and attentional functions in patients with rTLE. Furthermore, increased FC between the right cerebellar crus I and right inferior parietal lobule may exert a compensatory effect on executive deficits in patients with this pathological condition. In conclusion, these findings contribute to improving our understanding of the disrupted and compensatory characteristics of cerebellar–cerebral networks and attentional deficits in rTLE, and indicate that the cerebellum potentially represents an intervention target for delaying or improving clinical deficits in patients with TLE.

Conflict statement

No conflicts are declared.

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